Sleep Apnea Syndrome: Central Sleep Apnea and Pulmonary Hypertension Worsened during Treatment with Auto-CPAP, but Improved by Adaptive Servo-Ventilation

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Abstract

In this 71-year-old man diagnosed as obstructive sleep apnea syndrome initially, the apnea-hypopnea index in polysomnography was 31.3/hour. He started auto-adjusted continuous positive airway pressure (auto-CPAP) treatment in July 2005 but developed congestive heart failure in December 2007. Pulmonary arterial pressure (PAP), estimated by echocardiography, was 71 mmHg. In January 2008, during simplified sleep examination with a breath-movement sensor under auto-CPAP, many central-type apneas were recognized. After replacing auto-CPAP with adaptive servo-ventilation (ASV), the apnea-hypopnea index was 5.3/hour and PAP became 36 mmHg after 3 months. It was thought that the increase of PAP was due to long-term inadequate use of auto-CPAP.

Key words: sleep apnea syndrome, central sleep apnea, pulmonary hypertension, auto-adjusted continuous positive airway pressure (auto-CPAP), adaptive servo-ventilation (ASV)

(Inter Med 49: 415-421, 2010)
(DOI: 10.2169/internalmedicine.49.2461)

Introduction

Continuous positive airway pressure (CPAP) is an established therapy in sleep apnea syndrome (SAS), but the management of SAS after the initiation of CPAP involves not only attempting maintenance of the patient’s compliance, but also regular monitoring of the patient’s respiratory status during sleeping time, and, if required, re-titrating a prescribed pressure of CPAP and even considering to change the mode of ventilator. However, when we look at the present situation, it seems that respiratory monitoring tends to be negligent for patients with excellent compliance for the use of CPAP. Here, we report the case of a patient who was diagnosed as obstructive sleep apnea syndrome (OSAS) and developed congestive heart failure (CHF) with pulmonary hypertension (PH), central sleep apnea (CSA) and Cheyne-Stokes respiration (CSR) 2 years and 5 months after the start of auto-adjusted CPAP (auto-CPAP), but improved as a result of the change from auto-CPAP to adaptive servo-ventilation (ASV).

Case Report

A 71-year-old man who was a kimono dealer visited our department with the chief complaint of snoring in July 2005. As for his clinical history, in July 2004 (age 70), he underwent inpatient care in the neurology unit at the Hospital of Nippon Medical School, Tokyo, Japan, for cerebral infarction. One year after discharge from hospital, he developed weakness of the left upper and lower extremities; in July 2005 he was diagnosed as recurrence of cerebral infarction and was admitted to the hospital again. During hospitalization, he was noted by several medical workers to have a snoring problem and was referred to the respiratory internal medicine unit because SAS was suspected. As for his

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Received for publication May 11, 2009; Accepted for publication October 27, 2009
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past history, he was found to have hypertension at the age of 26 years and had an operation for sinusitis at age 39 years. At age 70 he had hypertensive heart failure, (as a result of cardiac catheterization performed by the division of cardiology) as well as hyperlipidemia and hyperuricemia. He was a non-smoker. On initial admission (July 2005), he was 164 cm tall and weighed 71 kg, with a body mass index of 26.4 kg/m². Subjective sleeping time in bed: 7-8 hours/day. Scores of Epworth sleepiness scale: 4 points. Findings upon chest X-ray: The cardiothoracic ratio (CTR) was 53.2%. The lungs and mediastinal space appeared normal. Electrocardiography (ECG) in awaking: Initially, Multifocal ventricular extra systole was seen. RR interval was regular. Holter’s ECG was not performed. Trans-thoracic echocardiography (TTE): Ejection fraction (EF), 20%; estimated pulmonary artery pressure (PAP), 34 mmHg; Mild mitral regurgitation (MR) was seen. Blood examination (normal range in parentheses): Complete blood count and biochemical test did not show aberration except that the serum creatinine (Cr) level was 1.23 mg/dL (≤1.2). Pulmonary function test: Vital capacity (VC), 3.92L; %VC, 121.4%; forced expiratory volume in one second (FEV₁), 2.75L and FEV₁/%VC, 72.4%; Sleep examination by portable monitor (SMPM): apnea-hypopnea index (AHI), 24.3/hour; Polysomnography (PSG): AHI was 31.3/hour, CSA developed 4.5/hour (<5/hour), and there was no Cheyne-Stokes respiration (CSR).

We diagnosed this patient as OSAS, which was treated using auto-CPAP (Auto-set S, Teijin Co, Tokyo, Japan) at a pressure of 4-15 cmH₂O. By the pharmacotherapy for cerebral infarction (ozagrel natrium and glicerin), the patient’s subjective symptoms improved, and he was discharged on the 16th day of hospitalization. The patient was considered to have good compliance with auto-CPAP because he regularly attended monthly visits to the pulmonary outpatient department in our hospital and when we reviewed the state of 30 days use of auto-CPAP recorded in a computer in auto-CPAP from late October 2005, auto-CPAP was used for 29 days and on average the usage time was 7 hours and 33 minutes per a day. The subjective symptom (snoring) was relieved, and AHI decreased to 9.6 from 24.3/hour on SSE while under auto-CPAP treatment, and 4% desaturation index and the ratio that the time that is oxygen saturation >90% accounted for in all examination time improved as well (shown in Fig. 1). However, the patient complained of dyspnea in mid-December 2007. He had a checkup in our hospital, and was diagnosed as having CHF, and was admitted to hospital for treatment.

Findings upon reexamination (December 2007): No change in standing height, body weight, or BMI in comparison with the initial assessment (July 2005), body temperature, 36.8°C; pulse, 120/minute and irregular; and blood pressure, 114/56 mmHg. Chest X-ray: CTR was 60%, and pulmonary artery expansion and pleural effusion pool were present on both sides. ECG: There were ventricular extra-systole and negative conversion of T waves in leads I, V₅, and V₆. Holter’s ECG: total beats, 62340; total sinus beats, 60255; HR 63 (Max111 Min39) VPC747 (isolated 557 couplet 10 triplet 2) SVPC1338(isolated 1191 couplet 10 triplet 4 run 1) TTE: EF, 23%; estimated PAP, 71 mmHg; and there was evidence of severe mitral regurgita-

Figure 1. The transition of findings of simplified sleep examination in all courses (1) 40 mg/day intravenously on the first day of hospitalization and 20 mg/day orally starting from the second day; (2) nitroglycerin was changed to a continuous infusion of 0.2 μg/kg/minute from a patch used before hospitalization, which was subsequently replaced by oral isosorbide (40 mg/day).
Table 1. The Findings of Sleep Examination by Portable Monitor (SEPM) with Breath-movement Sensor under Auto-CPAP

<table>
<thead>
<tr>
<th></th>
<th>OSA</th>
<th>CSA</th>
<th>MSA</th>
<th>Total apnea</th>
<th>Hypopnea</th>
<th>Apnea + hypopnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>1</td>
<td>126</td>
<td>1</td>
<td>128</td>
<td>71</td>
<td>199</td>
</tr>
<tr>
<td>AHI (hour)</td>
<td>0.1</td>
<td>16.9</td>
<td>0.1</td>
<td>17.1</td>
<td>9.5</td>
<td>26.7</td>
</tr>
<tr>
<td>Average time (min’ sec”)</td>
<td>0’32”</td>
<td>0’25”</td>
<td>0’26”</td>
<td>0’25”</td>
<td>0’46”</td>
<td>0’33”</td>
</tr>
<tr>
<td>Maximum time (min’ sec”)</td>
<td>0’32”</td>
<td>0’39”</td>
<td>0’26”</td>
<td>0’39”</td>
<td>1’31”</td>
<td>1’31”</td>
</tr>
</tbody>
</table>

Average SpO2: 96%
Minimum SpO2: 88%
Duration of SpO2 ≤95%: 111’42” (24.9%)
Duration of SpO2 ≤90%: 2’36” (0.8%)

*the temporal ratio when the SpO2 was under 90%

We administered furosemide (40 mg/day intravenously on the first day of hospitalization and from the second day, 20 mg/day orally), and CHF initially improved but then worsened on the fifth day, and we replaced nitroglycerin administered with patch with continuous infusion (0.2 μg/kg/minute), and subsequently changed to oral isosorbide (40 mg/day). Furthermore, we started β-blocker, bisoprolol fumarate (2.5 mg/day) on the fifth day but discontinued after one day because of aggravation of CHF. As a result of the above-mentioned pharmacotherapy, CHF was improved. Based on the patient’s clinical course, pulmonary function testing and a radioisotope examination, it was difficult to imagine that chronic obstructive pulmonary disease, pulmonary thromboembolism, collagen disease or vascular disease which could be the cause of PH, so that we thought that exacerbation of SAS might be causing PH in spite of the use of auto-CPAP. Therefore, we performed SEPM with chest and abdominal breath-movement band sensors (Morpheus R⩭; Teijin Co., Tokyo, Japan) while the patient was using CPAP when the symptoms of CHF (subjective symptom, clinical observation and X-ray’s findings etc.) had stabilized at the end of January 2008. After that, the patient was discharged in February 2008. The results of SEPM with breath-movement band sensors were shown in Table 1 and Fig. 2. During the examination time period, AHI was 26.7/hour and 126 CSA events of 128 total apneas were present, so that we confirmed that the patient developed CSR. We considered that auto-CPAP was inadequate as a treatment for SAS in this patient and therefore decided to change the ventilator to ASV (Auto-Set CS⩭, Teijin Co, Tokyo, Japan) in March 2008, and set the expiratory end pressure at 5 cmH₂O and the support pressure at 3-10 cmH₂O. The respiratory rate of back-up was 15/min when apnea of the patient continued for a long time. The setting was adjusted automatically according to the standard mode of the apparatus.

We show the waveforms of breath movement and airflow in the PSG at the ASV initiation in Fig. 3 and show the findings of PSG at the diagnosis of OSAS [(a) in Table 2], those using ASV at the ASV initiation [(b) in Table 2] and those one year and five months after the initiation which was performed in a nearby clinic of sleep medicine because PSG could not be performed in our hospital at the time [(c) in Table 2]. At (b), AHI and the index of CSA which were 5.3 and 0 respectively improved remarkably in comparison with those at (a) which were 31.3 and 4.5 respectively, and at (c), they were 5.0 and 0 respectively, which meant the improvement was maintained. But at (b), %stageN3 which means the proportion of hours that stages 3 and 4 in non-rapid eye movement sleep accounts for the decrease from 9% at (a) to 1.6% and at (c), it became 0. The transition of findings of SEPM in all courses is shown in Fig. 1. Under ASV, AHI was 0.8 and 4% desaturation index was 1.7, which means both of them improved compared to the values under auto-CPAP (9.6 and 6.1). The transition of findings of TTE and serum BNP is shown in Fig. 4. Serum BNP (normal value ≤18.4 pg/mL) was improved to 11.8 pg/mL in September of the same year, that is, after 6 months of ASV initiation, compared to 143.8 pg/mL in February 2008, that is, just before the ASV induction. In March 2009, after 12 months of ASV initiation, it was 8.3, which means the improvement was maintained. When comparing the findings of TTE results recorded in December 2007, April 2008 (one
The findings of the movement of breathing and airflow in SEPM with breath-move-ment sensor under auto-CPAP. Central sleep apnea (CSA) and tachypnea appear in turn, which means Cheyne-Stokes respiration (CSR).

The findings of breathing exercise and airflow in PSG under ASV. It is obvious that CSA and CSR disappeared by using ASV.

As for the transition of pharmacotherapy for heart failure, we reduced furosemide (20–10 mg/day) in March 2008 when ASV was initiated. We did not change the pharmacotherapy until October 2008. And in November 2008, we stopped administering furosemide, started benazepril (5 mg/day) which is angiotensin converting enzyme inhibitor, and changed angiotensin inhibitor for the combination of losartan-hydrochlorothiazide (1 tablet/day) and irbesartan (50 mg/day) from Olmecartan (20 mg/day). The reason for the change of drugs was the exacerbation of renal dysfunction (the serum creatinine level grew above 1.4 mg/dL), not due to heart failure. In addition, severe MR was found on Doppler UCG of December 2007, but, as for the MR, it was thought to be a secondary change caused by heart failure rather than the cause of it so that the degree of regurgitation was improved in reexamination after three months from initiation of ASV.
Table 2. (a) the Findings of PSG at Time of Initial Diagnosis. (b) the Findings of PSG while Using Adaptive Servo-ventilation (ASV) at the Initiation of ASV. (c) The Findings of PSG while Using ASV 1 Year and 5 Months after the Initiation of ASV

<table>
<thead>
<tr>
<th></th>
<th>(a)</th>
<th>(b)</th>
<th>(c)</th>
<th>(a)</th>
<th>(b)</th>
<th>(c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in bed (min)</td>
<td>653</td>
<td>591</td>
<td>585</td>
<td>4.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sleep period time (min)</td>
<td>576.5</td>
<td>519</td>
<td>561.5</td>
<td>0.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>440.5</td>
<td>371.5</td>
<td>347</td>
<td>20.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>16.5</td>
<td>67</td>
<td>23.5</td>
<td>6.1</td>
<td>5.3</td>
<td>5</td>
</tr>
<tr>
<td>Sleep efficacy (%)</td>
<td>76.4</td>
<td>71.6</td>
<td>61.8</td>
<td>31.3</td>
<td>5.3</td>
<td>5</td>
</tr>
<tr>
<td>% Wake</td>
<td>23.6</td>
<td>28.4</td>
<td>38.2</td>
<td>92</td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td>% Stage N1</td>
<td>27.4</td>
<td>5.5</td>
<td>16.9</td>
<td>70</td>
<td>92</td>
<td>89</td>
</tr>
<tr>
<td>% Stage N2</td>
<td>27.4</td>
<td>47.2</td>
<td>34.2</td>
<td>18.5</td>
<td>12.8</td>
<td>5.5</td>
</tr>
<tr>
<td>% Stage N3</td>
<td>6.8</td>
<td>1.2</td>
<td>0</td>
<td>3% Desaturation index</td>
<td>31.3</td>
<td>4.3</td>
</tr>
<tr>
<td>% Stage R</td>
<td>14.8</td>
<td>17.7</td>
<td>10.7</td>
<td>SpO2&lt;90% (%)</td>
<td>29.2</td>
<td>0</td>
</tr>
</tbody>
</table>

MSA: mixed sleep apnea, min: (*), minutes: sec (*): seconds, SpO2: pulse oximetry

Discussion

It is well known that SAS is often accompanied by left ventricular failure and pulmonary hypertension and that CSA and CSR are caused by circulatory disease. As for the mechanism of the former effect, it is thought that intrapleural pressure is usually negative, that the degree of negative pressure is strengthened by apnea or hypopnea during sleep, and that SAS exposes the heart to increased preload and afterload (1). Regarding CSA and CSR caused by circulatory disease, the circulating blood flow rate becomes slower because of the delayed response to changes in blood gas pressure and pH, and increased regulation of blood pH by chemoreceptors (2). In the present case, OSA and CSA appeared within the background of the patient’s medical history of sinusitis and left ventricular failure, which were reflected in the mixture of OSA and CSA found upon the initial PSG. Because we confirmed the presence of many central respiratory events after the pharmacotherapy of CHF based on SEPM with breath-movement band sensors, not PSG, we were not able to precisely grasp the transition.
However the number of CSAs seen in the finding of Morpheus R® in January 2008 was as about four times that in the initial PSG in July 2005 and a manifest CSR which could not be seen in the initial PSG. Therefore, it was supported that in this patient, the central respiratory disturbance would have worsened during the 2 years and six months and that those would be the causes of heart failure rather than the result, because numerous CSAs and CSR were still seen in the sleep examination when the symptoms of heart failure had already improved.

Boudewyns and coworkers reported a case of OSAS increased by CSA after initiation of auto-CPAP, and they proposed three possible causes: the induction of arousal events related to pressure variations during auto-CPAP, the triggering of an inhibitory upper respiratory tract reflex by a rise of CPAP pressure, and the emergence of CSA with the decrease of OSA by CPAP (3). And according to Lehman and coworkers’ study, there were more than 5 per hour of CSAs in PSGs at titration in 13% of the OSAS patients for whom they prescribed CPAP, and the risk factors of an exacerbation of CSA were man, the presence of CSA in baseline PSG, and a medical history of heart failure (4); the present patient had all of these factors. Therefore, there is a possibility that the inadequate use of auto-CPAP exacerbated the central respiratory disturbance. We are reflecting on the fact that we had judged that auto-CPAP had been used appropriately by the patient, based on the patient’s feeling of use and the improvement of AHI by portable monitor under using auto-CPAP without seeing a change of CSA. We are considering that in a patient of OSAS with heart failure, the effect of CPAP including auto-CPAP should be determined by PSG, not by a portable monitor, and that it is necessary to follow up a respiratory status including a central respiratory event during sleep at regular intervals afterwards. But, for the setting an interval of the follow-up, we would have to accumulate data evaluated by PSG of time transitions of efficiencies of CPAP in patients of SAS with heart failure.

ASV corrects unstable respiratory status, and although expiratory end pressure is constant, the support pressure is automatically regulated from data of spontaneous respiration of the patient analyzed by pneumotachograph in ASV during inspiration, becoming higher when the patient’s respiratory rate decreases and becoming lower when that increases, which is expected that ASV would allow intrapleural pressure to stabilize and enable heart load to improve. The setting mentioned above was performed according to a standard mode of ASV automatically and used in the past study about Auto-Set CS® (5). On changing a mode of ventilator, we also considered a change to fixed-pressure CPAP or biventricular positive airway pressure (BLPAP) other than ASV. The efficacies for CSA with these modes of respiratory support apparatus have been discussed in previous studies (6, 7). However Buckle and coworkers reported that they did not find significant improvement in CSR by CPAP therapy in patients with heart failure (8), and Johnson and Johnson pointed out that BLPAP often rather exacerbated CSR or CSA (9). Therefore, we do not think that fixed-pressure CPAP and BLPAP are superior to ASV. When Teschner and coworkers weighed the efficacy of ASV, BLPAP, CPAP and nocturnal oxygenation, in an effect to decrease CSR, the ASV was significantly superior to CPAP and nocturnal oxygenation and equal to BLPAP, and in most cases, ASV was the most comfortable in all modes (10). However, at present, the evidence that heart failure can be improved by this treatment is derived from case reports or small-scale investigation (11); a large-scale clinical study has not yet been performed. Accumulation and analysis of cases treated using ASV is necessary in the future.

In the present case, we thought that ASV would have contributed to improvement of heart failure because the estimated PAPs on UCG measured at 1, 3 and 6 months after the ASV initiation were clearly decreased, and serum BNP levels measured at 2 and 6 months after the initiation improved in comparison with that at the time of initiation although we reduced furosemide at the time of initiation and then did not change the pharmacotherapy for 8 months. But in the PSG, %StageN3 decreased after the ASV initiation, which gave the impression that sleep quality was rather worsened under ASV even considering that this patient is an elderly man and that the last PSG was performed in another place. We should continue to investigate the influence that ASV has on sleep quality in the future, although we have the policy to continue ASV in this patient based on his feeling of the usefulness of ASV and since the influence of ASV on his cardiac function is better than CPAP. In addition, one of the problems of ASV is that it is about six times more expensive than CPAP in Japan. This patient bears only 10% of medical care expense because of his medical insurance, but still he has to pay 8,730 yen to our hospital every month to use ASV though CPAP costs only 1,460 yen every month. Fortunately, he does not show dissatisfaction economically. However, the problem of expense should be overcome because it will become a large barrier and block the beneficial spread of the use of ASV.

References

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